SUPPLEMENT ARTICLE

Efficacy of Antimicrobial Therapy for *Mycoplasma genitalium* Infections

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Mycoplasma genitalium **has been causally linked with nongonococcal urethritis in men and cervicitis, pelvic inflammatory disease, preterm birth, spontaneous abortion, and infertility in women, yet treatment has proven challenging. To inform treatment recommendations, we reviewed English-language studies describing antimicrobial susceptibility, resistance-associated mutations, and clinical efficacy of antibiotic therapy, identified via a systematic search of PubMed supplemented by expert referral. Minimum inhibitory concentrations (MICs) from some contemporary isolates exhibited high-level susceptibility to most macrolides and quinolones, and moderate susceptibility to most tetracyclines, whereas other contemporary isolates had high MICs to the same antibiotics. Randomized trials demonstrated poor efficacy of doxycycline and better, but declining, efficacy of single-dose azithromycin therapy. Treatment failures after extended doses of azithromycin similarly increased, and circulating macrolide resistance was present in high levels in several areas. Moxifloxacin remains the most effective therapy, but treatment failures and quinolone resistance are emerging. Surveillance of *M. genitalium* prevalence and antimicrobial resistance patterns is urgently needed.**

Keywords. *Mycoplasma genitalium*; drug resistance; antimicrobial; sexually transmitted diseases; therapeutics.

Since 1980, when *Mycoplasma genitalium* was first identified [1], evidence of its association with reproductive tract disease syndromes has been slowly accumulating. Not surprisingly, the majority of these studies have been conducted in men, as the organism was first detected in men with nongonococcal urethritis (NGU). This evidence is strong and consistent, with an approximately 5.5-fold increased risk of NGU among men [2], and *M. genitalium* is an accepted cause of male urethritis. There has been some debate over the role of *M. genitalium* in female reproductive tract disease, and there are relatively few data on some syndromes (eg, female urethritis, ectopic pregnancy, birth outcomes). However, a recent meta-analysis demonstrated an approximately 2- to 2.5-fold increase in the risk of cervicitis, pelvic inflammatory disease (PID), infertility, and preterm delivery for women infected with *M. genitalium* [3].

This recognition of *M. genitalium* as a pathogen is coupled with an increasing awareness of significant challenges with respect to treatment of *M. genitalium* infections, and concerns about the efficacy of the standard syndromic treatment regimens [4]. To inform the US Centers for Disease Control and Prevention (CDC) sexually transmitted diseases (STDs) treatment guidelines, we reviewed the literature on the antimicrobial susceptibility of *M. genitalium* and treatment efficacy. Our review was guided by 6 key questions: (1) What is the antimicrobial resistance profile of *M. genitalium*? (2) Is azithromycin 1 g superior to doxycycline 100 mg twice daily for 7 days? (3) Is a longer course of azithromycin superior to a single 1-g dose of azithromycin? (4) What is the efficacy of moxifloxacin? (5) What is the preferred therapy for *M. genitalium*? (6) Should the recommended therapy for STD syndromes be altered in recognition of the role of *M. genitalium*?

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METHODS

In May 2015, we identified literature on the antimicrobial susceptibility and treatment efficacy for *M. genitalium* by searching PubMed using the following search terms: ([mycoplasma AND genitalium] OR [*M. genitalium*]) AND (treatment OR antibiotic). Scientific abstracts from professional meetings were also searched, and expert referral identified newly published articles not yet indexed. Articles were included if they reported results of minimum inhibitory concentration (MIC) testing, detection of resistance mutations by sequencing, or resolution of symptoms (clinical cure) and/or eradication of *M. genitalium* (microbiologic cure) after antibiotic treatment. Articles published in languages other than English were excluded, as were reviews and commentaries. Where 2 reports of the same study population were identified, we selected only the most complete report. The search yielded 265 articles, of which we excluded 196 after title review, and a further 16 after abstract review. There were 46 reports with data on in vitro susceptibility or detection of resistance-mediating mutations and 39 with data on treatment outcomes (6 articles provided data on both).

RESULTS

In Vitro Antimicrobial Susceptibility

Performing in vitro antimicrobial susceptibility testing for *M. genitalium* is challenging because the organism is slow-growing in culture media and cultivating clinical isolates is extremely difficult [5]. As a result, the majority of studies that have assessed MICs for various antibiotics have done so on a limited number of *M. genitalium* isolates, obtained either from the American Type Culture Collection (ATCC), or from colleagues that have succeeded in isolating clinical strains and shared them within the scientific community. Very few strains have been adapted to grow axenically, and either G37 (the type strain) or several additional isolates available from ATCC that are genetically indistinguishable from G37 have been frequently used to determine MICs. However, since 2005, clinical *M. genitalium* strains have been isolated more frequently using tissue culture in Vero cells [6], and MICs to several antimicrobials have been performed on a wider variety of clinical isolates.

To date, MICs have been performed for a total of 13 antibiotic classes (Table 1) overall [6–24], and investigators have evaluated the antimicrobial susceptibility of contemporary clinical isolates to 4 of these classes: ketolides, macrolides, quinolones, and tetracyclines [20, 22–24]. Given the absence of a cell wall in *M. genitalium*, antibiotics that inhibit cell wall synthesis or disrupt its integrity (eg, β-lactams, glycopeptides) are inherently ineffective and, with few exceptions, MICs for these antibiotics have not been assessed. Aminoglycosides, as well as spectinomycin, rifampin, linezolid, and second-generation quinolones class I (eg, norfloxacin, lomefloxacin) have all demonstrated MICs >1.0 μg/mL [8, 9, 19, 20]. In contrast, contemporary MICs for most macrolides, other quinolones, and most tetracyclines vary widely, ranging from highly susceptible (MIC < 0.01 μg/mL) to suggestive of resistance (MIC ≥2.0 μg/mL). Initial MICs for the new fluoroketolide solithromycin (CEM-101) performed on 5 isolates in 2009 suggested that the organism should be highly susceptible to the drug (≤0.00032 μg/mL) [19]. A more recent study evaluated solithromycin MICs in a panel of 40 *M. genitalium* strains (25 macrolide susceptible and 15 macrolide resistant) and found that MICs in macrolide-susceptible strains indicated good susceptibility (≤0.001–0.002 μg/mL), but were higher for macrolide-resistant strains (0.25–16 μg/mL), and that 20% of macrolide resistant strains had MICs >2 μg/mL [24].

Efficacy of Antimicrobials for *M. genitalium* Infection

CDC-Recommended Therapies

Either doxycycline 100 mg twice daily for 7 days or azithromycin 1 g in a single dose is recommended for the treatment of NGU and cervicitis. Seven observational studies have evaluated eradication of *M. genitalium* after a 7- to 9-day course of doxycycline [25–31], and 18 have evaluated microbiologic cure rates after treatment with 1 g of azithromycin [21, 26, 28–43] (Table 2). Microbiologic cure rates (eradication) after doxycycline varied widely from 17% to 94%, whereas microbiologic cure rates achieved with azithromycin 1 g were fairly consistent in observational studies prior to 2008, ranging from 72% to 100% [26, 28, 30, 32–36, 40]. However, they were lower in more recent studies, ranging from 50% to 91% [21, 29, 31, 37–39, 41–43]. Three randomized controlled trials (RCTs), typically considered the highest level of evidence, have compared azithromycin and doxycycline therapy in men with urethritis and demonstrated substantially lower cure rates for both antimicrobials (Figure 1). Although 2 of the 3 trials found that azithromycin was superior to doxycycline for microbiologic cure of *M. genitalium* ($P = .002$ for both), cure rates for azithromycin ranged from 67% to 87% and 31% to 45% for doxycycline [51, 52]. The third and most recent RCT found no significant difference in the efficacy of azithromycin (1 g) and doxycycline and high levels of treatment failure with both regimens (40% vs 30%, $P = .41$) [58], suggesting that the efficacy of single-dose azithromycin therapy is declining.

Azithromycin Extended-Dose Therapy

No randomized trials have compared different azithromycin regimens, but 4 observational studies have compared the single-dose regimen to doses given over 5–7 days [29, 30, 35, 37]. Initial studies conducted in Sweden among patients who had experienced treatment failure after doxycycline suggested that a 1-g dose of azithromycin may be less effective than an

Table 1. Minimum Inhibitory Concentrations by Antibiotic Class for *Mycoplasma genitalium*

Class	Antibiotic	MIC Range (All Tested Isolates), μg/mL	MIC Range (Recent Clinical Isolates), μg/mL
Aminoglycosides	All[a]	10–>50	. . .
Amphenicols	Chloramphenicol	0.5–25	. . .
Aminocyclitols	Spectinomycin	1–5	. . .
Ketolides	Telithromycin	≤0.00003–0.015	. . .
	Solithromycin	≤0.0032–16	≤0.001–16
Lincosamides	All[b]	0.2–25	. . .
Macrolides	Erythromycin	≤0.001 to ≥16	0.03 to ≥16
	Clarithromycin	0.0005–128	0.016 to ≥16
	Azithromycin	≤0.000032–250	≤0.0002 to >64
	Other macrolides[c]	≤0.015–1	. . .
Monoxycarbolic acids	Mupirocin	0.25–1	. . .
Oxazolidinone	Linezolid	4–128	. . .
Pleuromutilins	Tiamutilin	0.0025–0.01	. . .
Quinolones	First generation[d]	0.06–32	. . .
	Second generation, class I[e]	1–64	. . .
	Second generation, class II[f]	0.063 to >16	0.5 to >16
	Third generation[g]	0.03–4	
	Fourth generation, all[h]	0.008 to >16	0.016 to >16
	Moxifloxacin	0.016 to >16	0.031 to >16
Rifamycins	Rifampin	32–64	. . .
Streptogramins	Pristinamycin	<0.01–0.02	. . .
Tetracyclines	Tetracycline	≤0.01–4	0.125–4
	Doxycycline	≤0.008–2.5	0.06–2
	Minocycline	≤0.01–2.5	. . .

All clinical isolates: includes data from references [6–24]. Recent clinical isolates: excludes MIC assessments on ATCC isolates and limited early clinical isolates that had been tested multiple times by different investigators [20, 22–24].

Abbreviation: MIC, minimum inhibitory concentration.

[a] Aminoglycosides include amikacin, netilmicin, gentamicin, kanamycin, neomycin, tobramycin, streptomycin.

[b] Lincosamides include clindamycin, lincomycin.

[c] Other macrolides include dirithromycin, flurithromycin, spiramycin, josamycin, miocamycin, roxithromycin.

[d] First-generation quinolones include nalidixic acid, garenoxacin.

[e] Second-generation quinolones class I include norfloxacin, lomefloxacin.

[f] Second-generation quinolones class II include ofloxacin, ciprofloxacin.

[g] Third-generation quinolones include sparfloxacin, grepafloxacin, tosufloxacin.

[h] Fourth-generation quinolones include gemifloxacin, trovafloxacin, gatifloxacin, moxifloxacin, sitafloxacin, DC-159a.

extended regimen given over 5 days (500 mg on day 1, followed by 250 mg daily for 4 days). In the first study, treatment efficacy was somewhat lower in patients who received the 1-g dose than in those who received the 5-day regimen (85% vs 96%, $P = .11$) [30], and in the second study there were no instances of treatment failure after the 5-day azithromycin regimen [29]. A subsequent larger observational study in Norway compared 3 dosing regimens: a single 1-g dose; 1 g followed by a second 1-g dose in 5–7 days; and 500 mg once followed by 250 mg daily for 4 days. In contrast, this nonrandomized comparison found little difference in the proportion of men who experienced microbiologic cure (79% vs 74% vs 78% of patients given the 3 regimens, respectively) [35]. Similarly, there were only small differences in microbiologic outcomes between a 1-g and a 2-g single dose in a Japanese observational study (86% vs 91%) [37]. Consistent with findings from the randomized trials, more recent reports after the extended courses of azithromycin [42, 63, 65] and single 2-g doses [61] have indicated relatively low levels of microbiologic cure (25%–81% and 73%, respectively), suggesting that the efficacy of azithromycin given at higher single doses or for longer duration may also be declining.

Moxifloxacin Therapy

No clinical trials have evaluated moxifloxacin as a therapy for *M. genitalium*, but it has been used in cases of treatment failure.

Table 2. *Mycoplasma genitalium* and Efficacy of Antimicrobial Therapy

Reference, First Author and Year	Design	Population	Outcome	Regimen	Treatment Efficacy
Horner 1993 [44]	Case series	N = 98 MG^+ British men with NGU attending an STD clinic Ages 19–53	Microbiologic cure[a] Follow-up (10–21 d)	Doxycycline (200 mg stat plus 100 mg/d × 13 d)	Doxycycline: 10/14 (71%) had microbiologic cure
Gambini 2000 [32]	Cohort	N = 52 MG^+ Italian men with NGU attending an STD clinic Ages 17–70	Microbiologic cure[a] Clinical cure[b] Follow-up (7 d)	Doxycycline (200 mg/d × 7 d) OR Azithromycin (1 g stat)	Doxycycline: 33/35 (94%) had clinical and microbiologic cure Azithromycin: 14/17 (82%) had clinical and microbiologic cure
Johannisson 2000 [45]	Case series	N = 21 MG^+ Swedish men with urethritis (n = 18) and women (n = 3) attending STD clinics Ages 18–60	Microbiologic cure[a] Clinical cure[b] Follow-up (3–4 wk)	Tetracycline (0.5 g 2 times/d × 10 d)	Tetracycline: Men: 5/13 (38%) had microbiologic cure, 7/13 (54%) had clinical cure Women: 0/1 (0%) had microbiologic cure
Horner 2001 [46]	Cohort	N = 109 MG^+ British men with NGU attending an STD clinic Age range NR	Clinical cure[b] Follow-up (2, 6, 12 wk)	Doxycycline (200 mg stat plus 100 mg/d × 13 d) OR Erythromycin (500 mg 4 times/d × 14 d) Persistent urethritis: Erythromycin (500 mg 4 times/d × 14 d) plus Metronidazole (400 mg 2 times/d × 5 d)	Doxycycline-erythromycin (combined): 0/7 (0%) had clinical cure
Maeda 2001 [47]	Cohort	N = 12 MG^+ Japanese men with NGU attending urology clinic Ages 17–69	Microbiologic cure[a] Clinical cure[b] Follow-up (14 d)	Levofloxacin (100 mg 3 times/d × 14 d)	Levofloxacin: 4/12 (33%) had microbiologic cure; 11/12 (92%) had clinical cure
Falk 2003 [25]	Cohort	N = 60 MG^+ Swedish men (n = 34) and women (n = 26) attending an STD clinic Age range NR	Microbiologic cure[a] Follow-up (4–5 wk)	Doxycycline (200 mg stat plus 100 mg × 8 d) OR Lymecycline (300 mg 2 times/d × 10 d) Asymptomatic MG^+: Azithromycin (500 mg stat plus 250 mg/day × 4 d)	Doxycycline-lymecycline (combined): 6/16 (38%) of men had microbiologic cure; 4/14 (29%) of women had microbiologic cure Azithromycin: 8/8 (100%) of men and women had microbiologic cure
Dupin 2003 [27]	Cohort	N = 9 MG^+ French men with urethritis attending an STD clinic Age range NR	Microbiologic cure[a] Clinical cure[b] Follow-up (15–28 d)	Doxycycline (100 mg/day × 7 d) OR Minocycline (100 mg/day × 7 d) OR Spectinomycin (2 g) AND Minocycline (100 mg/day × 7 d)	Doxycycline: 0/1 (0%) had microbiologic and clinical cure Minocycline: 3/7 (43%) had microbiologic cure; 5/7 (71%) had clinical cure Spectinomycin/minocycline: 1/1 (100%) had microbiologic or clinical cure
Taylor-Robinson 2004 [48]	Cohort	N = 16 MG^+ British men; with persistent NGU (n = 7) or recurrent NGU (n = 4) attending an STD clinic Age range 18–53	Microbiologic cure[a] Follow-up (NR)	Erythromycin 500 mg 4 times/d × 4–6 wk	Erythromycin: 9/11 (82%) had microbiologic cure

Table 2 continued.

Reference, First Author and Year	Design	Population	Outcome	Regimen	Treatment Efficacy
Bradshaw 2006 [34]	Case series	N = 34 MG^+ Australian men with NGU attending an STD clinic Ages 22–54	Microbiologic cure[a] Clinical cure[b] Follow-up (1 mo)	Azithromycin (1 g stat) Failures: Azithromycin (1 g weekly × 3) Azithromycin (weekly) failures: Moxifloxacin (400 mg bid × 10 d)	Azithromycin stat: 23/32 (72%) had microbiologic cure; 24/32 (75%) had partial clinical cure and recurrence Azithromycin weekly: 0/3 (0%) had microbiologic cure Moxifloxacin: 9/9 (100%) had microbiologic cure
Wikstrom 2006 [28]	Cohort	N = 38 MG^+ Swedish men with persistent urethritis (n = 32) and female partners (n = 6) attending an STD clinic initially treated with doxycycline (200 mg stat plus 100 mg/d × 8 d) Ages 19–47	Microbiologic cure[a] Clinical cure[b] Follow-up (3 wk)	Azithromycin (1 g stat OR 500 mg stat plus 250 mg/day × 4 d) OR Erythromycin (500 mg 2 times/d × 10 d) Female partners: Azithromycin (1.5 g × 5 d)	Azithromycin: 20/20 (100%) of men and 4/4 (100%) women had microbiologic cure; 18/20 (90%) of men had clinical cure, clinical cure for women NR Erythromycin: 2/5 (40%) of men had microbiologic cure; 2/11 (18%) had clinical cure
Ross 2006 [49]	Randomized double-blind multisite trial	N = 4 MG^+ European and South African women with PID Age range NR	Microbiologic cure[a] Follow-up (5–24 d and 28–42 d)	Moxifloxacin (400 mg/day × 14 d) OR Ofloxacin (400 mg 2 times/d) plus Metronidazole (500 mg 2 times/d × 14 d)	Moxifloxacin: 3/3 (100%) had microbiologic failure Ofloxacin/metronidazole: 1/1 (100%) had microbiologic cure
Stamm 2007 [40]	Randomized double-blind multisite trial	N = 42 MG^+ US men with NGU attending STD clinics Ages 18–45	Microbiologic cure[a] Clinical cure[b] Follow-up (5 wk)	Rifalazil (2.5 mg stat) OR Rifalazil (12.5 mg stat) OR Rifalazil (25 mg stat) OR Azithromycin (1 g stat)	2.5 mg Rifalazil: 0/5 (0%) had microbiologic cure; 2/8 (25%) had clinical cure 12.5 mg Rifalazil: 0/7 (0%) had microbiologic cure; 0/8 (0%) had clinical cure 25 mg Rifalazil: 0/5 (0%) had microbiologic cure; 2/5 (40%) had clinical cure Azithromycin: 6/7 (86%) had microbiologic and clinical cure
Haggerty 2008 [50]	Cohort	N = 88 MG^+ US women with PID attending outpatient clinics Ages 14–37	Microbiologic cure[a] Follow-up (30 d)	Inpatient: Cefoxitin (2 g parenterally every 6 h) plus doxycycline (100 mg 2 times/d × 14 d) Outpatient: Cefoxitin (2 g IM) plus probenecid (1 g) plus doxycycline (100 mg 2 times/d × 14 d)	Inpatient-outpatient (combined): Endometrium and/or cervix: 33/56 (59%) had microbiologic cure Endometrium: 18/32 (56%) had microbiologic cure

Table 2 continued.

Reference, First Author and Year	Design	Population	Outcome	Regimen	Treatment Efficacy
Björnelius 2008 [30]	Cohort	N = 159 MG^+ Norwegian and Swedish men with urethritis (n = 115) and women with cervicitis (n = 44) attending STD clinics Ages 18–61	Microbiologic cure[a] Clinical cure[b] Follow-up (20–56 d)	Doxycycline (200 mg stat plus 100 mg × 8 d) OR Azithromycin (1 g stat) Doxycycline failures: Extended azithromycin (500 mg stat plus 250 mg × 4 d) Azithromycin failures: extended doxycycline (100 mg 2 times/d × 15 d)	Doxycycline: 13/76 (17%) of men and 10/27 (37%) of women had microbiologic cure; 21/75 (28%) of men and 55/20 (25%) of women had clinical cure Azithromycin: 33/39 (85%) of men and 15/17 (88%) of women had microbiologic cure; 17/37 (46%) of men and 3/8 (38%) of women had clinical cure Extended azithromycin: 45/47 (96%) of men and 6/6 (100%) of women had microbiologic cure. Extended doxycycline: 2/3 (67%) of men and 0/1 (0%) of women had microbiologic cure.
Jernberg 2008 [35]	Cohort	N = 452 MG^+ Norwegian men with NGU (n = 234) and women with cervicitis (n = 218) attending STD clinics Age range NR	Microbiologic cure[a] Follow-up (4–5 wk)	Azithromycin (1 g stat) OR Azithromycin (1 g stat plus 1 g stat 5–7 d after 1st dose) OR Ofloxacin (200 mg bid × 10 d) OR Moxifloxacin (400 mg × 7 d) Asymptomatic MG^+: Azithromycin (500 mg plus 250 mg × 4 d)	Azithromycin 1 g: 144/182 (79%) had microbiologic cure Azithromycin 1 g × 2: 28/38 (74%) had microbiologic cure Azithromycin 5 d: 76/98 (78%) had microbiologic cure Ofloxacin: 4/9 (44%) had microbiologic cure Moxifloxacin: 3/3 (100%) had microbiologic cure
Bradshaw 2008 [36]	Cohort	N = 120 MG^+ Australian men with urethritis (n = 102) and women with cervicitis (n = 18) attending an STD clinic Age range NR	Microbiologic cure[a] Follow-up (1 mo)	Azithromycin (1 g stat) Failures: Moxifloxacin (400 mg × 10 d)	Azithromycin: 101/120 (84%) had microbiologic cure Moxifloxacin: 11/11 (100%) had microbiologic cure
Mena 2009 [51]	Randomized trial	N = 78 MG^+ US men with NGU attending an STD clinic Age range NR	Microbiologic cure[a] Clinical cure[b] Follow-up (1st: 10–17 d; 2nd: 31–41 d)	Doxycycline (100 mg 2 times/d × 7 d) Azithromycin (1 g stat) OR Failures: Azithromycin (500 mg stat plus 250 mg/day × 4 d)	Doxycycline: 14/31 (45%) had microbiologic cure; 21/31 (68%) had clinical cure Azithromycin: 3/23 (87%) had microbiologic cure; 17/23 (74%) had clinical cure Failures: 3/5 (60%) had microbiologic cure; 4/5 (80%) had clinical cure
Thurman 2010 [31]	Cohort	N = 182 MG^+ US women (n = 125) with bacterial STI and male partners (n = 57) attending an STD clinic Age 14–45	Microbiologic cure[a] Follow-up (30 d)	Doxycycline (100 mg bid × 7 d) Azithromycin (1 g stat)	Doxycycline: 7/8 (88%) of men and 14/14 (100%) of women had microbiologic cure Azithromycin: 45/49 (92%) of men and 99/111 (89%) of women had microbiologic cure

Table 2 continued.

Reference, First Author and Year	Design	Population	Outcome	Regimen	Treatment Efficacy
Schwebke 2011 [52]	Randomized trial (double blind)	N = 54 MG^+ US men attending 4 urban STD clinics Age 16–45	Microbiologic cure[a] Follow-up (1st: 15–19 d; 2nd 35–40 d)	Azithromycin (1 g stat; with or without tinidazole) OR doxycycline (100 mg 2 times/d × 7 d with or without tinidazole)	Azithromycin: 30/45 (67%) had microbiologic cure Doxycycline: 12/39 (31%) had microbiologic cure
Takahashi 2011 [53]	Cohort	N = 4 MG^+ Japanese men attending urology clinics Age ≥18	Microbiologic cure[a] Clinical cure[b] Follow-up (1–3 wk)	Levofloxacin (500 mg × 7 d)	Levofloxacin: 3/5 (60%) had microbiologic cure; 2/4 had clinical cure (50%)
Hamasuna 2011 [54]	Cohort	N = 18 MG^+ Japanese outpatient men Age ≥20	Microbiologic cure[a] Clinical cure[b] Follow-up (2–3 wk)	Gatifloxacin (200 mg 2 times/d × 7 d)	Gatifloxacin: 15/18 (83%) had microbiologic cure; 43/43 (100%) had clinical cure
Hagiwara 2011 [21]	Cohort	N = 30 MG^+ Japanese men with NGU attending urology clinics Age range NR	Microbiologic cure[a] Clinical cure[b] Follow-up (2–4 wk)	Doxycycline (100 mg bid × 14 d for azithromycin failures Azithromycin (1 g stat) Gatifloxacin (7 d; dose not specified) for patients with both azithromycin and doxycycline failure	Doxycycline: 1/2 (50%) had microbiologic cure Azithromycin: 25/30 (83%) had microbiologic cure Gatifloxacin: 1/1 (100%) had microbiologic cure.
Yew 2011 [55]	Cross-sectional	N = 9 MG^+ New Zealand men with recurrent NGU Age range NR	Microbiologic cure[a] Follow-up (34–58 d)	Azithromycin (1 g stat) Azithromycin (500 mg plus 250 mg on days 2 & 5)	Azithromycin-1 g: 2/3 (67%) had microbiologic cure Azithromycin-day 1, 2, 5: 3/5 (60%) had microbiologic cure
Ito 2012 [56]	Case series	N = 11 MG^+ Japanese men with NGU attending outpatient clinic Age 16–69	Microbiologic cure[a] Follow-up (35 d)	Sitafloxacin (100 mg 2 times/d × 7 d)	Sitafloxacin: 11/11 (100%) had microbiologic cure; 11/13 (85%) had clinical cure.
Terada 2012 [37]	Cohort	N = 257 MG^+ Japanese women with cervicitis attending women's clinic Age 18–42	Microbiologic cure[a] Follow-up (14 d after completing therapy)	Azithromycin 1 g single dose (n = 42) Azithromycin 2 g single dose (n = 21) Clarithromycin 400 mg × 7 d (n = 20) Clarithromycin 400 mg × 14 d (n = 20) Moxifloxacin 400 mg × 7 d (n = 42) Moxifloxacin 400 mg × 14 d (n = 42) Levofloxacin 500 mg × 7 d (n = 22) Levofloxacin 500 mg × 14 d (n = 21) Sitafloxacin 200 mg × 7 d (n = 14) Sitafloxacin 200 mg × 14 d (n = 13)	Azithromycin 1 g: 36/42 (86%) had microbiologic cure Azithromycin 2 g: 19/21 (91%) had microbiologic cure Clarithromycin 7 d: 13/20 (65%) had microbiologic cure Clarithromycin 14 d: 17/20 (85%) had microbiologic cure Moxifloxacin 7 d: 38/42 (91%) had microbiologic cure Moxifloxacin 14 d: 42/42 (100%) had microbiologic cure Levofloxacin 7 d: 12/22 (55%) had microbiologic cure Levofloxacin 14 d: 15/21 (71%) had microbiologic cure Sitafloxacin 7 d: 11/14 (79%) had microbiologic cure Sitafloxacin 14 d: 12/13 (92%) had microbiologic cure

Table 2 continued.

Reference, First Author and Year	Design	Population	Outcome	Regimen	Treatment Efficacy
Gesink 2012 [57]	Cross-sectional	N = 26 MG^+ residents of Greenland with MRMM Age 15–65	Microbiologic cure Follow-up NR	Moxifloxacin 400 mg × 7 d	Moxifloxacin: 26/26 (100%) had microbiologic cure.
Twin 2012 [38]	Cross-sectional	N = 111 MG^+ Australian men (n = 86) and women (n = 25) attending sexual health center treated with 1 g azithromycin. Age range NR	Microbiologic cure[a] Follow-up (14–127 d)	Azithromycin (1 g stat) Moxifloxacin (400 mg × 10 d) for azithromycin treatment failures	Azithromycin: 77/111 (69%) had microbiologic cure Moxifloxacin: 77/77 (100%) had microbiologic cure
Manhart 2013 [58]	Randomized trial (double blind)	N = 65 MG^+ US men with NGU attending STD clinic Age ≥16	Microbiologic cure[a] Clinical cure Follow-up (2–5 wk)	Doxycycline (100 mg bid × 7 d) Azithromycin (1 g stat)	Doxycycline: 8/27 (30%) had microbiologic cure; 13/27 (48%) had clinical cure Azithromycin: 15/38 (40%) had microbiologic cure; 24/38 (63%) had clinical cure
Walker 2013 [39]	Cohort	N = 41 MG^+ Australian women attending primary, family planning, and sexual health clinics Age 16–25	Microbiologic cure[a] Follow-up (4 wk)	Azithromycin (1 g stat) Moxifloxacin (400 mg × 10 d) for Azithromycin treatment failures	Azithromycin: 29/32 (91%) had microbiologic cure Moxifloxacin: 3/3 (100%) had microbiologic cure
Anagrius 2013 [29]	Retrospective case series	N = 313 MG^+ specimens archived in Sweden Age NR	Microbiologic cure[a] Clinical cure Follow-up (up to 52 wk)	Doxycycline (200 mg on day 1 plus 100 mg × 9 d) Azithromycin (1 g stat) Azithromycin (500 mg on day 1 plus 250 mg × 4 d) as primary treatment for 35 patients and after doxycycline treatment failure for 72 patients Moxifloxacin (400 mg × 7 d) for azithromycin treatment failures	Doxycycline: 35/91 (38%) of men and 38/80 (46%) of women had microbiologic cure; 31/141 (22%) of men and women had clinical cure Azithromycin 1 g: 57/65 (88%) of men and 50/52 (96%) of women had microbiologic cure; 43/80 (54%) of men and women had clinical cure Azithromycin 5 d: 13/14 (93%) of men and 12/12 (100%) of women had microbiologic cure; 15/21 (71%) of men and women had clinical cure Moxifloxacin: 9/9 (100%) had microbiologic cure
Manhart 2013 [66]	Cohort	N = 37 MG^+ US men with microbiologic treatment failure in a randomized trial Age ≥16	Microbiologic cure[a] Follow-up (6 or 9 wk)	Doxycycline (100 mg bid × 7 d) for azithromycin treatment failures (n = 20) Azithromycin (1 g stat) for doxycycline treatment failures (n = 17) Moxifloxacin (400 mg × 7 d) for treatment failures	Doxycycline: 6/20 (30%) azithromycin failures had microbiologic cure at 6 wk Azithromycin: 12/17 (71%) doxycycline failures had microbiologic cure at 6 wk Moxifloxacin: 17/20 (85%) had microbiologic cure at 6 or 9 wk
Couldwell 2013 [60]	Cohort	N = 26 MG^+ Australian patients attending sexual health clinic Age NR	Microbiologic cure[a] Follow-up (NR)	Azithromycin (1 g stat) Moxifloxacin (400 mg × 10 d) for treatment failures	Azithromycin: 12/26 (46%) had microbiologic cure Moxifloxacin: 9/13 (69%) had microbiologic cure
Henning 2014 [41]	Cohort	N = 5 MG^+ Australian youth attending primary care clinic Age 16–24	Microbiologic cure[a] Follow-up (1 mo)	Azithromycin (1 g stat)	Azithromycin: 1/2 (50%) had microbiologic cure

Table 2 continued.

Reference, First Author and Year	Design	Population	Outcome	Regimen	Treatment Efficacy
Kikuchi 2014 [61]	Retrospective cohort	N = 29 MG^+ specimens from Japanese men with NGU attending a urology clinic Age range NR	Microbiologic cure[a] Follow-up (4 wk)	Azithromycin (2 g single dose) Sitafloxacin: 100 mg bid × 7 d Levofloxacin: 500 mg × 7 d	Azithromycin: 11/15 (73%) had microbiologic cure Sitafloxacin: 33/33 (100%) had microbiologic cure Levofloxacin: 0/1 (0%) had microbiologic cure
Gundevia 2015 [42]	Retrospective cohort	N = 218 MG^+ Australian men (n = 144) & women (n = 74) attending sexual health center Age 15–57	Microbiologic cure[a] Follow-up (4 wk)	Azithromycin (1 g stat) Azithromycin (1 g stat plus 500 mg daily × 4 d) Doxycycline (dose not specified) Moxifloxacin (dose not specified)	Azithromycin 1 g: 64/87 (74%) had microbiologic cure Azithromycin 5 d: 10/15 (67%) had microbiologic cure Doxycycline: 2/5 (40%) had microbiologic cure Moxifloxacin: 5/6 (83%) microbiologic cure
Bissessor 2015 [43]	Cohort	N = 155 MG^+ Australian men (n = 112) & women (n = 43) attending sexual health center Age 18–41	Microbiologic cure[a] Follow-up (28 d)	Azithromycin (1 g) Moxifloxacin (400 mg daily × 10 d) for azithromycin failures Pristinamycin (1 g 4 times/d × 10 d) for moxifloxacin failures	Azithromycin: 95/155 (61%) had microbiologic cure Moxifloxacin: 53/60 (88%) had microbiologic cure Pristinamycin: 6/6 (100%) had microbiologic cure
Guschin 2015 [62]	Cohort	N = 46 MG^+ Russian men with urethral symptoms or unprotected sex attending STI clinic	Microbiologic cure[a] Follow-up (10–14 d)	Josamycin 500 mg 3 times/d × 10 d Moxifloxacin 400 mg × 10 d for treatment failures	Josamycin: 43/46 (94%) had microbiologic cure Moxifloxacin: 3/3 (100%) had microbiologic cure
Unemo 2015 [63]	Cohort	N = 85 MG^+/CT^+ Norwegian men with NGU (n = 31) and women with cervicitis (n = 54) attending STI clinic Age 18–51	Microbiologic cure[a] Follow-up (5 wk)	Azithromycin 500 mg on day 1 plus 250 mg × 4 d	Azithromycin: 64/79 (81%) had microbiologic cure
Hook 2015 [64]	Randomized trial	N = 10 MG^+ US men with gonorrhea enrolled in multisite trial Age 19–53	Microbiologic cure[a] Follow-up (7 d after enrollment)	Solithromycin 1000 mg (five 200-mg capsules) single dose Solithromycin 1200 mg (six 200-mg capsules) single dose	Solithromycin 1000 mg: 1/3 (33%) had microbiologic cure Solithromycin 1200 mg: 6/7 (87%) had microbiologic cure

Abbreviations: bid, twice daily; CT, *Chlamydia trachomatis*; IM, intramuscular; MG, *Mycoplasma genitalium*; MRMM, macrolide resistance-mediating mutation; NGU, nongonococcal urethritis; NR, not reported; PCR, polymerase chain reaction; PID, pelvic inflammatory disease; stat, immediately; STD, sexually transmitted disease; STI, sexually transmitted infection.

[a] Microbiologic cure defined as absence of DNA or RNA by PCR or transcription-mediated amplification in urine, urethral or cervical swab, or biopsy specimens at follow-up.

[b] Clinical cure defined as absence of signs at follow-up [29, 30, 34, 45, 58]; absence of symptoms at follow-up [27, 28, 47]; signs and/or symptoms at follow-up [21, 32, 40, 46, 51]; or not defined [65].

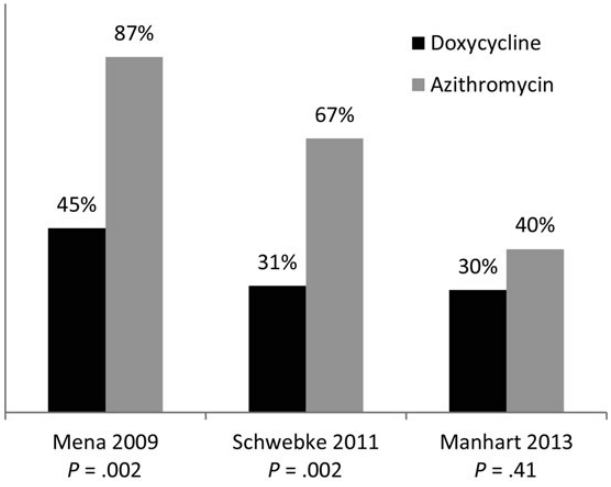

Figure 1. Randomized controlled trials comparing the efficacy of doxycycline (100 mg bid x 7 days) vs azithromycin (1 g single dose) for the treatment of *Mycoplasma genitalium* infections.

A total of 15 studies have reported on treatment outcomes from persons who received moxifloxacin (400 mg × 7–14 days) after azithromycin and/or doxycycline treatment failed to eradicate the organism (Figure 2). Early studies published from 2008 to 2012 observed no cases of clinical or microbiologic treatment failure following moxifloxacin therapy [29, 34–36, 38, 39, 49, 57]. However, more recent studies have reported cases of *M. genitalium* persistence after moxifloxacin therapy, with microbiologic cure rates ranging from 69% to 100% [37, 42, 43, 60, 62, 66]. A Japanese study observed 4 treatment failures among 42 men (9%) after a 7-day regimen of moxifloxacin, whereas there were no treatment failures among 42 men after the 14-day regimen [37], leading some to speculate that the longer regimen would be more effective. However, subsequent studies have reported treatment failures after the 10-day regimen, suggesting that duration of therapy may not influence treatment success [42, 43, 60].

Other Antimicrobials

Older quinolones are not highly active against *M. genitalium*, with microbiologic cure rates ranging from 55% to 71% for levofloxacin (500 mg × 7 or 14 days) [37, 53] to as low as 44% for ofloxacin (200 mg twice daily × 10 days) [35]. Several newer quinolones have been evaluated in Japan where microbiologic cure rates for gatifloxacin (200 mg twice daily × 7 days) were 83%–100% [21, 54] and ranged from 79% to 100% for sitafloxacin (200 mg × 7 or 14 days) [37, 56, 61]. Josamycin (500 mg 3 × day × 10 days) had a cure rate of 94% among 46 Russian STD clinic attendees [62], and pristinamycin (1 g 4 × day for 10 days) successfully eradicated *M. genitalium* after moxifloxacin treatment failure in 6 of 6 Australian men treated with the drug [43], but neither josamycin nor pristinamycin is available in the United States. Data on the clinical efficacy of solithromycin in *M. genitalium*–infected individuals are limited to a small number of men who received single-dose therapy to treat *Neisseria gonorrhoeae*, and microbiologic cure rates ranged from 33% for the 1000-mg dose to 87% for the 1200-mg dose [64].

Therapy for Pelvic Inflammatory Disease

Only 1 study, the PID Evaluation and Clinical Health (PEACH) study, has evaluated the efficacy of the recommended therapy for PID: cefoxitin (2 g) parenterally every 6 hours and doxycycline (100 mg) orally twice a day for 14 days, or cefoxitin (2 g) intramuscularly plus probenecid (1 g) orally, then doxycycline (100 mg) orally twice a day for 14 days. Of *M. genitalium*–positive women with PID treated with this regimen, 41% experienced microbiologic failure [50], indicating low effectiveness against *M. genitalium*. Alternate PID regimens include other antimicrobials known to have poor efficacy against *M. genitalium* (tetracyclines, lincosamides, penicillins, nitroimidazoles), suggesting that currently recommended therapies for PID inadequately cover *M. genitalium*. A very small number of women with *M. genitalium*–associated PID receiving a 14-day regimen of moxifloxacin (n = 3) and 1 woman receiving a 14-day combined ofloxacin plus metronidazole regimen experienced microbiologic cure [49]. However, these regimens have not been tested in larger groups of women.

Antibiotic Resistance Mutations Detected by Sequencing

Macrolide Resistance-Mediating Mutations

Advances in sequencing technology permit the detection of single-nucleotide polymorphisms in region V of the 23S ribosomal RNA gene of *M. genitalium* that prevent macrolide binding. A total of 19 studies have evaluated the presence of macrolide resistance-mediating mutations (MRMMs) in individuals testing positive for *M. genitalium* (Figure 3) [23, 29, 38, 43, 55, 57, 59, 60, 61, 65, 67–74, 77]. In the initial report of the detection of these MRMMs, 7 of 9 individuals who experienced treatment failure after 1 g azithromycin expressed a resistance mutation only in the isolates obtained following treatment failure, but not in pretreatment strains [22], suggesting that selective pressure resulted in the emergence of resistant organisms. Across all studies, the prevalence of MRMMs in pretreatment specimens ranged from 20% to 100%, but was substantially higher in posttreatment specimens, ranging from 44% to 57%. Notably, however, posttreatment specimens were primarily from individuals already having failed therapy. In studies that tested banked specimens, irrespective of when in the course of treatment they were collected, the prevalence of MRMMs was somewhat lower, ranging from 4% to 38%.

Macrolide resistance appears to be increasing over time. In Australia, where the 1-g single dose is standard, azithromycin

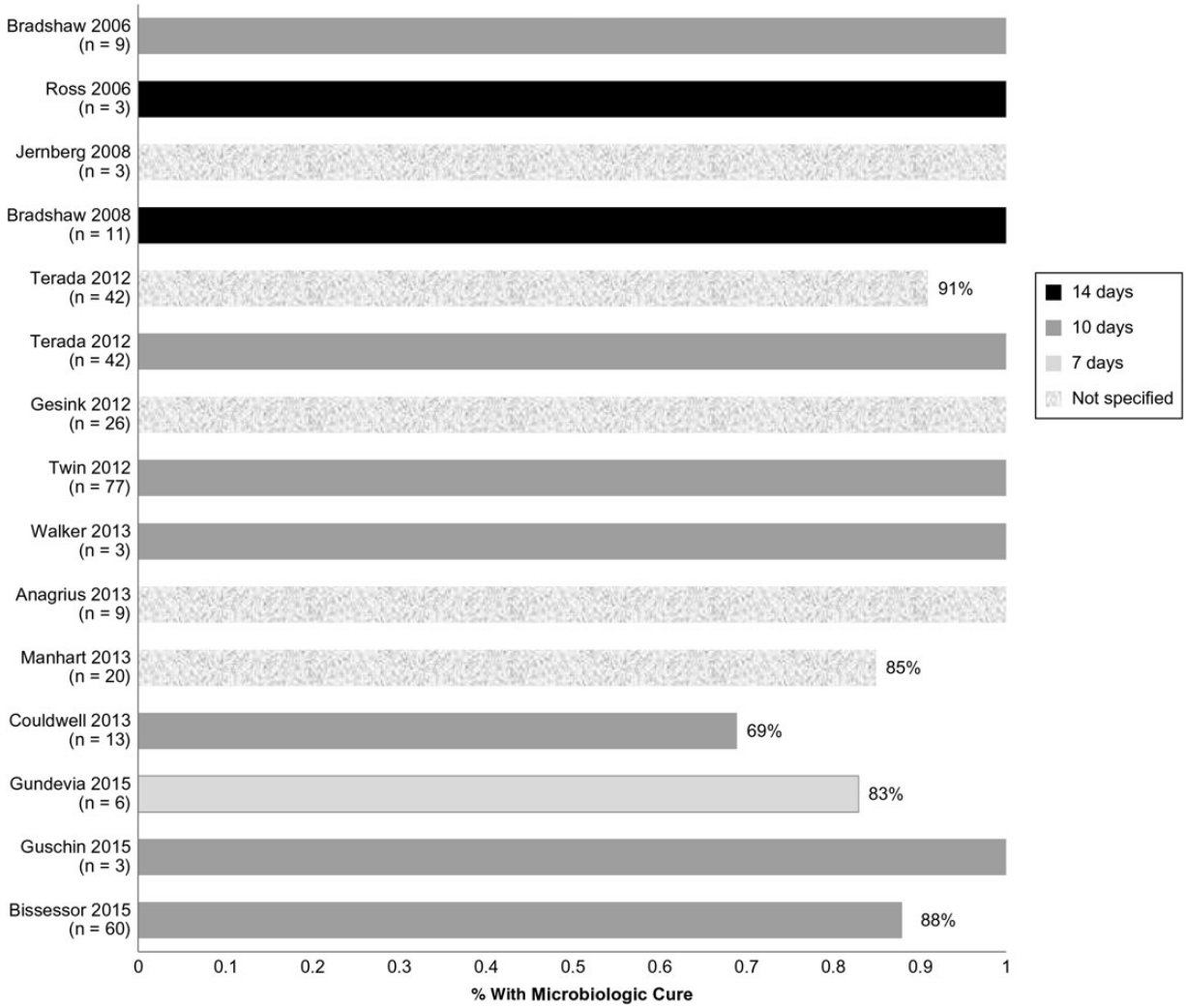

Figure 2. Summary of treatment outcomes after moxifloxacin (400 mg × 7, 10, or 14 days), n = total number given moxifloxacin.

cure rates declined from 84% in 2005–2007 to 69% in 2007–2009, and only 55% of the pretreatment specimens from individuals with treatment failure were susceptible to azithromycin [38]. In Sweden and Japan, no macrolide resistance was detected in *M. genitalium*–positive specimens from early time periods (2006–2007 and 2011, respectively), but MRMMs were found in 21% and 29% of specimens in later time periods (2011 and 2013, respectively) [29, 61]. Data from Sweden suggest that the extended dose of azithromycin might reduce the risk of selection for macrolide resistance. Among 7 patients failing the 1-g single dose of azithromycin, pretreatment specimens had no MRMMs, but mutations were detected in specimens from all 7 patients after therapy. In contrast, only 1 of 26 (3.8%) patients treated with the extended regimen experienced treatment failure, and resistance mutations were detected in that individual's pretreatment specimen [29]. Although suggestive of slower emergence of resistance with the extended dose, this represents a limited number of treated patients, most of whom had failed prior doxycycline treatment, and further data are needed.

Quinolone Resistance-Determining Region Mutations

A total of 5 studies have evaluated the presence of mutations in *gyrA* and *parC* in the quinolone resistance-determining region of *M. genitalium*–positive specimens from small numbers of patients [72, 75–78]. Overall, *parC* mutations were the most commonly detected, found in 5%–37% of tested specimens. Two studies that paired the detection of *gyrA* or *parC* mutations with treatment outcomes suggest that these mutations are associated with treatment failure. In Japan, posttreatment specimens of 4 *M. genitalium*–positive patients who had failed gatifloxacin therapy contained mutations in *gyrA* or *parC*, whereas no mutations were present in 2 of the pretreatment specimens [78]. In

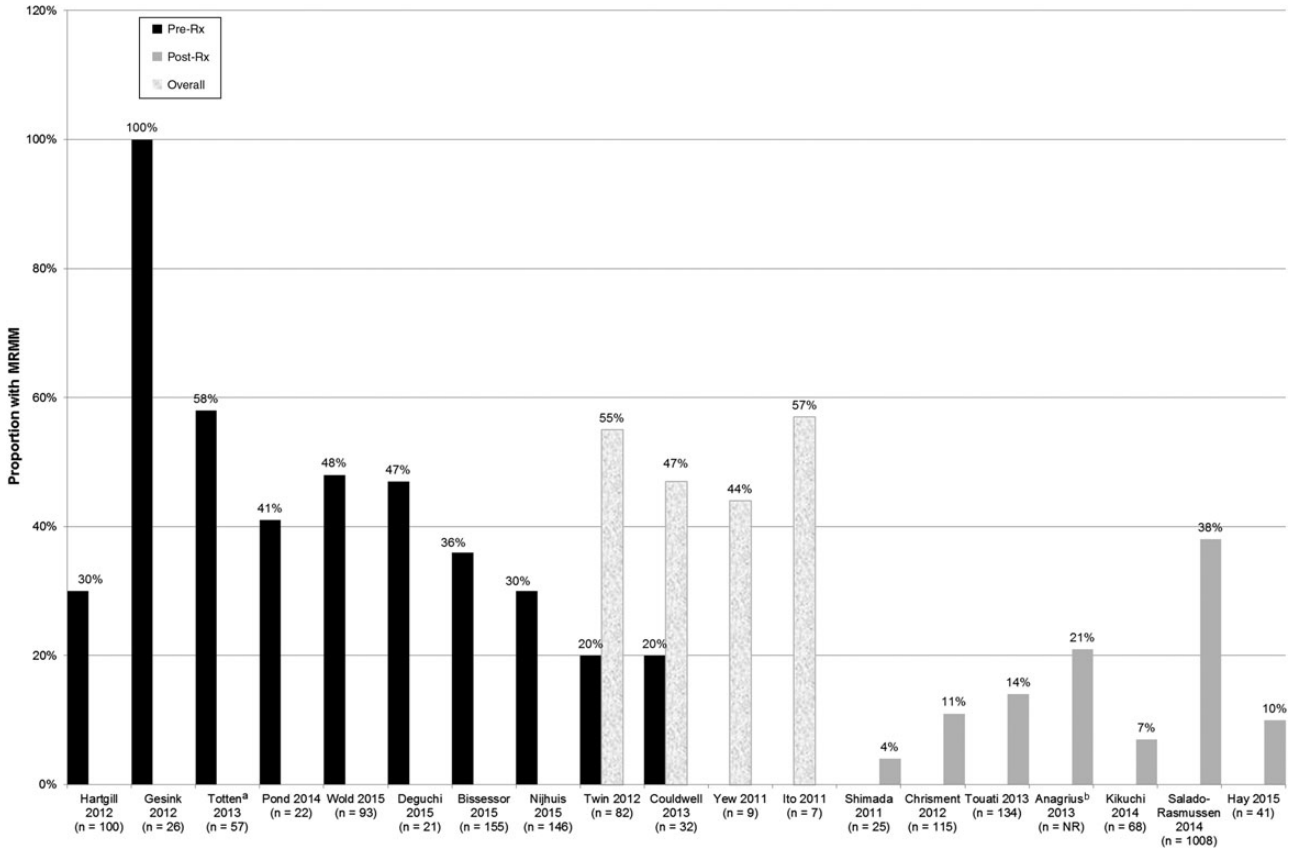

Figure 3. Proportion of *Mycoplasma genitalium*–positive specimens with macrolide resistance mediating mutations (MRMMs), n = total number tested. [a]Based on minimum inhibitory concentration (MIC) ≥8 μg/mL for Azithromycin; [b]Data from 2011 only; NR = not reported.

33 Australian patients, mutations were significantly associated with treatment failure after moxifloxacin (4/4 with mutations vs 0/9 without mutations, $P = .005$) [60]. Combined resistance may also be emerging, as 6 strains with combined macrolide and moxifloxacin resistance have been isolated in culture (Jensen, unpublished data).

DISCUSSION

This systematic review of the published literature describing the antimicrobial susceptibility of *M. genitalium* and treatment efficacy for existing antibiotics revealed substantial challenges for the treatment of this sexually transmitted pathogen. MICs from some contemporary *M. genitalium* isolates exhibited high-level susceptibility to most macrolides and some quinolones, and reasonable susceptibility to tetracyclines, but other contemporary isolates had high MICs to the same antibiotics, suggestive of resistance. RCTs confirmed observational data demonstrating poor efficacy of doxycycline and better but declining efficacy of single-dose azithromycin therapy. Data comparing extended doses of azithromycin to single-dose therapy were somewhat inconsistent, but the most recent studies suggest that the risk of treatment failure with longer durations of azithromycin therapy is similarly rising, perhaps as a result of the emergence of more widespread macrolide-resistant *M. genitalium*. Moxifloxacin remains the most effective drug licensed in the United States for the treatment of infections caused by *M. genitalium*, but reports of treatment failure and quinolone resistance are emerging. Two agents not available in the United States. (pristinamycin and sitafloxacin) demonstrated high rates of *M. genitalium* eradication in small studies and hold some promise. Solithromycin, another new agent, was effective in a small number of men at high doses, but high MICs to this drug in macrolide-resistant strains suggest that optimism for this new agent should remain cautious.

Despite MICs indicating susceptibility to doxycycline, it often fails to eradicate *M. genitalium* from >50% of infected individuals and the reasons for this are unclear. Existing evidence indicates that single-dose azithromycin therapy is superior to doxycycline therapy in the treatment of *M. genitalium* in most settings. Nevertheless, the efficacy of the 1-g dose of

azithromycin is not consistently high and appears to be declining. In many geographic areas, cure rates are only fair and have at no point reached the 95% threshold below which the identification of alternate therapies is recommended [79]. While the efficacy of a longer course of azithromycin appears to be similar to the efficacy of the single 1-g dose, an extended azithromycin regimen may be less likely to select for resistance in areas where macrolide resistance is rare. However, the extended regimen would likely not result in high levels of cure in areas where a high proportion of circulating *M. genitalium* strains already harbor MRMMs. Given the rapid emergence of antimicrobial resistance subsequent to the adoption of single-dose therapies for *N. gonorrhoeae*, combination therapy employing 2 antimicrobials is now recommended. A similar approach may be warranted for other STIs that have demonstrated rapid emergence of resistance, such as *M. genitalium*.

Moxifloxacin is clearly superior to other treatments for *M. genitalium* available in the United States. However, this conclusion is based on a relatively small number of cases, the drug has not been tested in clinical trials, and the assessment of resistance markers in circulating strains has revealed mutations that have been associated with moxifloxacin treatment failures. Limited data suggest that, similar to macrolide resistance, quinolone resistance is selected for subsequent to treatment with fluoroquinolones. In addition to concerns about the emergence of quinolone resistance, therapy is relatively prolonged, there remains a relative paucity of data on the drug for treatment of *M. genitalium*, and it has been associated with liver toxicity. Therefore, despite good efficacy against *M. genitalium*, moxifloxacin should be used sparingly and only in cases of azithromycin treatment failure.

Given the rapid emergence of resistance to azithromycin and the potential emergence of resistance to moxifloxacin, antimicrobial resistance in *M. genitalium* should be monitored, and assays to do so have been developed. Initial detection of MRMMs required a 2-step process, beginning with polymerase chain reaction (PCR) amplification and detection followed by sequencing [80]. However, since that time, assays that perform simultaneous detection of *M. genitalium* infection and the presence of MRMMs are available. A rapid high-resolution melt analysis assay had 90% sensitivity relative to sequencing [38], and a real-time PCR assay based on fluorescence resonance energy transfer and melting curve analysis exhibited somewhat lower sensitivity (77%) [70]. In settings with access to the MRMM PCR detection assay, cases of treatment failure should be assessed for azithromycin resistance. Ideally, such assays would be implemented wherever *M. genitalium* testing is conducted and used to guide appropriate therapy. Similar single-step assays to detect quinolone resistance are needed.

Management of *M. genitalium* infections is complicated by the current lack of a US Food and Drug Administration (FDA)–approved assay. Clinical trials to seek FDA approval for *M. genitalium* diagnostic assays are planned, but until approval is secured, most treatment will be via syndromic therapy for NGU, cervicitis, and PID in settings without access to validated diagnostic testing for *M. genitalium*.

Mycoplasma genitalium appears to be responsible for 15%–20% of cases of NGU [81], and average clinical cure rates for NGU of any etiology were 74%–75% after doxycycline and 69%–80% after azithromycin [52, 58] in the most recent clinical trials. Although these cure rates are not ideal, the relative contribution of *M. genitalium* to NGU is not sufficiently large to warrant a change to those therapies. Among women with cervicitis, the prevalence of *M. genitalium* has ranged from 8% to 29% (with 1 exception) [81], yet the most commonly detected organism in cases of cervicitis remains *Chlamydia trachomatis*. Therefore, the currently recommended therapies for cervicitis are likely to be adequate in most cases. Some researchers advocate for azithromycin as the preferred agent for NGU and cervicitis, based on its superiority to doxycycline in the treatment of *M. genitalium*. Others, concerned about single-dose azithromycin inducing *M. genitalium* resistance, advocate for doxycycline as the preferred therapy for NGU and cervicitis, with extended-dose azithromycin given to persons with clinical treatment failure [29]. The choice of therapy will depend on the standard of care in each clinic setting, ideally informed by the local prevalence of *M. genitalium*—particularly *M. genitalium* harboring MMRM—among cases of NGU and cervicitis. Unfortunately, this information is rarely known, highlighting the need for better surveillance data on the causes of common STD syndromes and antimicrobial resistance patterns.

Cross-sectional studies suggest that *M. genitalium* is responsible for 12%–41% of persistent or recurrent NGU cases, and numerous clinical studies have documented that failure to eradicate *M. genitalium* is associated with persistent urethritis. Therefore, in settings with no access to diagnostic and resistance testing, revised treatment recommendations indicate that clinicians should treat persistent or recurrent urethritis with moxifloxacin. In settings with diagnostic but not resistance testing, persons diagnosed with *M. genitalium* should have tests of cure performed 3 weeks after therapy, and men with persistent detection of *M. genitalium* should be treated with moxifloxacin. Although data on the optimal duration of moxifloxacin therapy are not available, the 2015 CDC STD treatment guidelines recommend a 7-day regimen. However, some experts contend that short-course treatments have promoted the rapid emergence of antimicrobial resistance that we now confront, and prefer a 14-day regimen of moxifloxacin.

The prevalence of *M. genitalium* in women with PID ranges from 4% to 22% [81] and was lower than the prevalence of *C. trachomatis* and *N. gonorrhoeae* in the PEACH study (6.5% vs 14% for *C. trachomatis* and 15% for *N. gonorrhoeae*) as well

as in a multicenter study in Europe and South Africa (3.6% vs 42% for *C. trachomatis* and 31.3% for *N. gonorrhoeae*) [49]. The relatively low prevalence of *M. genitalium* in women with PID in most settings suggests that existing regimens should continue to be employed in primary cases of PID, despite their inconsistent activity against *M. genitalium*,. However, in the most recent study of US women with acute PID, *M. genitalium* prevalence was 22% and higher than either *C. trachomatis* (14%) or *N. gonorrhoeae* (7%) [82]. Should additional data support the finding that almost a quarter of PID cases may be caused by *M. genitalium*, this approach may need to be reconsidered. Where *M. genitalium* testing is available and the organism is detected in women diagnosed with PID, moxifloxacin 400 mg daily for 14 days has been effective [49]. Where testing is not available, clinicians should consider *M. genitalium* in cases that fail to respond to therapy and may treat with moxifloxacin.

This evaluation of published studies is characterized by several strengths and limitations. We searched the literature systematically, increasing the likelihood that we would identify all relevant data on this topic. Nevertheless, it is still possible that some data were not captured in our search and are not included here. We erred on the side of completeness and included conference abstracts, which often have minimal detail to judge study quality. Data from these sources may be less reliable than data from peer-reviewed publications. In some cases, few data were available to guide recommendations, particularly with respect to comparisons of the single-dose and extended regimens for azithromycin, or the duration of moxifloxacin therapy, and additional data will be required before definitive conclusions can be drawn.

This systematic review revealed decreasing susceptibility of *M. genitalium* to several key antibiotics, increasing treatment failure rates, and emerging resistance to both macrolides and quinolones. Nevertheless, the dominant perspective of members of the CDC treatment guidelines review group was that a national change in therapy for STD syndromes to specifically direct treatment toward the eradication of *M. genitalium* is not warranted at this time. Diagnostic testing for *M. genitalium* is becoming increasingly available and should be used to guide or adapt treatment decisions whenever possible, particularly when treating persons with persistent or recurrent NGU, cervicitis, or PID. Given the increasing spread of macrolide and quinolone resistance, there is an urgent need to implement surveillance to monitor *M. genitalium* prevalence and antimicrobial resistance patterns, and to develop new, more effective therapies for this increasingly recognized pathogen.

Notes

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